REMARKS

Claims 1, 3-5 and 7-12 stand rejected under 35 U.S.C. 102(b) as anticipated by Yata (EP 0091502). Claim 7 stands rejected under 35 USC 103(a) as obvious over Yata. Claim 13 stands rejected under 35 USC 103(a) as obvious over Yata and Bachynsky *et al.* (US Patent 5190748). Applicants respectfully traverse. However, solely to expedite prosecution, claim 1 has been amended to recite that the polar active substance and the organic alkalizing agent are combined with each other to form a hydrophobic conjugate as supported by, for example, original claim 9. No new matter is added.

The subject invention as defined by the amended claim 1 is directed to a pharmaceutical composition for oral absorption of a polar active substance, consisting essentially of: (a) ceftazidime as a polar active substance having a bioavailability of less than 30% which is poorly absorptive through lipid membranes because of its high hydrophilicity and charged ion; (b) an amino acid as an organic alkalizing agent having an amino acid or polyol structure which shows alkalinity in aqueous solution and is ionically bonded to the polar active substance; and (c) at least one surfactant having a C_{6-18} fatty acid structure which has an HLB (Hydrophilic-Lipophilic Balance) value of 4 to 18, wherein the polar active substance and the organic alkalizing agent are combined with each other to form a **hydrophobic conjugate**.

As described in the specification of the subject application, a first feature of a composition according to the subject invention is that the anionic moiety of the polar active substance is ionically bonded to the cationic moiety of the organic alkalizing agent. Accordingly, the charge of the active substance is neutralized to form relatively hydrophobic units composed of the active substance and the organic alkalizing agent. These hydrophobic units are agglomerated with each other to form a relatively hydrophobic conjugate, which is a thermodynamically stabilized form in an aqueous phase (outer phase). A second feature is that a surfactant having a fatty acid structure is added to the hydrophobic conjugate to transport the active substance through the lipid membranes. Since the

surfactant consists of a hydrophobic fatty acid moiety and a non-ionic hydrophilic moiety, it increases the surface activity between the conjugate and the lipid membranes without negatively affecting the ionic bonds formed in the conjugate, and induces the oral absorption of the drug through the lipid membranes of the whole gastrointestinal tract. In addition, since the surfactant makes the hydrophobic conjugate small and stable, it provides conditions advantageous for the penetration of the drug through the biological membranes (see Fig. 1).

Accordingly, a characteristic feature of the subject invention is that the polar active substance (ceftazidime) and the organic alkalizing agent (amino acid) are combined with each other to form a **hydrophobic conjugate**, which becomes smaller and stabilized by the addition of surfactant, and easily transported through the lipid membranes. Formation of such a hydrophobic conjugate, for example a conjugate having a size of 10nm to 100μm in water phase (claim 9), enables a great increase in the **oral** absorption rate of polar active substances which have been difficult or impossible to administer via the oral route. Thus, the present invention represents a high value-added technology.

Yata (EP 0091502 A1) is directed to a pharmaceutical preparation of cephalosporin for rectal administration which comprises an oleaginous base, a third generation cephalosporin, an amino acid and an ether type nonionic surfactant. In the preparation of Yata, an ether type nonionic surfactant is added to increase the absorbed amount of cephalosporin, and an amino acid is added to moderate a tissue-damaging action of the ether type nonionic surfactant (see page 3, lines 4-9) and to increase the absorbability of cephalosporin in an oleaginous base. There is no requirement in Yata for the amino acid be an organic alkalizing agent, and it can be a neutral, basic or acidic amino acid (see page 10, lines 15-17). This demonstrates the difference between the composition disclosed therein and the presently claimed invention.

The subject invention results in an increase in absorption rate in the whole gastrointestinal tract when administered via an oral route by decreasing polarity of the polar active substances. In contrast, Yata utilizes a composition for a rectal administration route for increasing absorption rate without changing polarity of active substances.

Because polar active substances have difficulty in transcellular penetration, there have been a number of studies of paracellular penetration of polar active substances, one of which is Yata. In Yata, rectal drug delivery is accomplished due to the presence of Peyer's patches which are lymphoid tissue or lymphoid module of large pore on the walls of small intestine and to the loose membrane structure of large intestine. That is, absorption of polar active substances may be increased through paracellular penetration rather than transcellular penetration. Further, an ether type nonionic surfactant such as polyoxyethylene alkyl ether can function to enlarge the loose membrane structure, which further enables paracellular penetration of polar active substances in Yata.

In the subject invention, the anionic moiety of polar active substance is ionically bonded to the cationic moiety of the organic alkalizing agent (an amino acid) to form a hydrophobic conjugate. This conjugate may then be transported through the lipid membranes in the entire intestines due to the markedly reduced polarity. That is, an alkalizing agent such as an appropriate amino acid is utilized to reduce polarity of the polar active substance and allow formation of a hydrophobic conjugates in the subject invention. In contrast, Yata teaches that an amino acid is simply added to moderate a tissue-damaging action of the ether type nonionic surfactant. At least because of the differences in compositional structure and function described above, Yata can neither anticipate the present invention nor render it obvious. Accordingly, the rejection should be withdrawn.

The Examiner has indicated that properties such as the size of the ceftazidime-amino acid complex (that is, hydrophobic conjugate) are inherent to the composition, even though Yata does not explicitly teach the property. Applicant respectfully submits that at least the reasons described below demonstrate that there is no hydrophobic conjugate formed in Yata.

As mentioned above, hydrophobic conjugates of the present invention are formed by ionic bonding of the anionic moiety of polar active substance and the cationic moiety of the organic alkalizing agent (an amino acid). That is, hydrophobic conjugates cannot be formed if there is no appropriate amino acid or if one uses a cationic form of an amino acid, such as an addition salt of the acid, for example a hydrochloride. As shown in Experiments and Examples of Yata, the blood

concentrations of cephalosporins increase only because of the addition of polyoxyethylene alkyl ether without the need for addition of amino acids (see Tables 2 and 3). Such results (increase of absorption rate without the addition of amino acid) clearly show that there is no hydrophobic conjugate of polar active substance and amino acid formed in Yata. Further, as also shown in Tables 2 and 3, the concentrations of cephalosporins in blood increase with the addition of Valine hydrochloride or Lysine hydrochloride (where the cationic moiety is covered by acid; that is, the amino acid cation is formed from the added HCl rather than from the cephalosporins.) Such results (increase of absorption rate with the addition of amino acid in which cationic moiety is covered) show that there is no hydrophobic conjugate formed in Yata. Accordingly, the composition of Yata does not have the property of forming hydrophobic conjugates (ceftazidime-amino acid complex) in intestinal juice and a different composition is formed. Thus, the present claims can not be anticipated or obvious in view of Yata.

Considering the above, even though Yata discloses a composition containing a third generation cephalosporin, an amino acid and an ether type nonionic surfactant, it neither describes nor suggests the characteristic feature of the subject invention. Specifically, Yata does not disclose a composition where the polar active substance and the organic alkalizing agent are combined with each other to form a **hydrophobic conjugate.** Yata also does not disclose, teach or suggest the advantageous effect resulting from this characteristic feature, that is, a great increase in the **oral** absorption rate of polar active substances. The compositions of Yata do not necessarily result in the composition of the present invention nor in a composition having properties of the present invention,. Accordingly, the presently claimed properties cannot be inherent in Yata and Yata neither anticipates nor renders obvious the subject invention.

Bachynsky *et al.* (US Patent 5190748) is directed to a method for treating a bacterial infection in a mammal, which comprises orally administering to the mammal a therapeutic amount of a pharmaceutical composition comprising a cephalosporin and an absorption enhancing amount of a two-component absorption enhancing system including a compound of the formula, $CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOH$ and a pharmaceutically acceptable salt of caprylic acid. In

Bachynsky *et al.*, it is described that the composition is coated with a pharmaceutically acceptable enteric coating material.

Even though Bachynsky *et al.* mentions an oral administration and enteric coating, it neither describes, teaches nor suggests the characteristic feature of the subject invention, i.e., the polar active substance and the organic alkalizing agent combined with each other to form a **hydrophobic conjugate,** and the advantageous effect resulting from the characteristic feature, i.e., a great increase in the **oral** absorption rate of polar active substances. Accordingly, Bachynsky *et al.* adds nothing to Yata that would render obvious the subject invention.

Considering the above, neither of the cited references teaches, discloses or suggests the characteristic features of the subject invention. Accordingly, the references cited by the Examiner, whether alone or in combination, neither explicitly nor inherently disclose, teach, or suggest the subject invention. For at least these reasons, the rejection of claims 1, 3-5 and 7-13 must be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Accordingly, Applicants request that the Examiner issue a Notice of Allowance indicating the allowability of claims 1, 3-5 and 7-13 and that the application be passed to issue. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Please charge any necessary fees that are not included herewith or credit any overpayment to deposit account no. 22-0261.

Respectfully submitted,

Date: 3 September 2008

/Keith G. Haddaway/

Keith Haddaway, Ph.D.
Registration No. 46,180
VENABLE
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 344-4000
Telefax : (202) 344-8300

980709